REMARKS

35 USC Section 112, first paragraph

Claim 21 remains rejected under 35 USC Section 112, first paragraph. The Examiner urges that the specification teaches HER2 antibody as a HER2 antagonist capable of treating breast cancer, but does not teach how to make any other antagonist that could be used in the treatment step of the claim.

Applicants have amended claim 21 by the incorporation of claim 24 therein (hence the cancellation of claim 24 as moot, and the amendment of the dependency of claim 25). Claim 21 now concerns therapy with a "HER2 antibody." The specification enables the production of, and therapy with, a HER2 antibody. Reconsideration and withdrawal of the Section 112, first paragraph enablement rejection is respectfully requested.

On page 4 of the above Office Action, claim 21 is rejected under 35 USC Section 112, first paragraph as failing to comply with the written description requirement. The Examiner urges that the specification provides evidence for only one species of antagonist, a HER2 antibody.

The amendment of claim 21 to refer to a HER2 antibody obviates the written description rejection. Reconsideration and withdrawal of the Section 112, first paragraph written description rejection is respectfully requested.

35 USC Section 112, second paragraph

Claims 21, and 24-26 are rejected under 35 USC Section 112, second paragraph as being indefinite. The Examiner urges that the preamble of claim 21 is drawn to a method of identifying a patient disposed to respond favorably to a HER2 antagonist, and the active step of the amended claim says "detecting" then "treating."

Claim 21 is amended herein to recite "identifying and treating a patient" in the preamble. Reconsideration and withdrawal of the Section 112, second paragraph rejection is requested.

35 USC Section 103

Claims 21, 24 and 26 are rejected under 35 USC Section 103 as being unpatentable over any one of Pauletti *et al.* *Oncogene* 13: 63-72 (1996); Ross *et al.* *Cancer* 79(11):2162-2170 (1997) (Ross II); or Persons *et al.* *Annals. Of Clinical and Laboratory Science* 30(1):41-48 (2000) for the detection step, and over any one of Ross *et al.* *Stem Cell* 16:413-428 (1998) (Ross I); Baselga *et al.* *J. Clin. Oncol.* 14(3): 737-744 (1996); Baselga *et al.* *Semin. Oncol.* 4(12): 78-83 (1999) for the treating step. Claim 25 is rejected under 35 USC Section 103(a) as being unpatentable over any one or more of Pauletti *et al.*, Persons *et al.*, or Ross II for the determination step as applied to claims 21, 24 and 26, and further in view of Baselga *et al.* (1999).

The Examiner urges that any one of Pauletti *et al.*, Ross II, or Persons *et al.* teaches HER2 gene amplification using FISH is superior to IHC for assessing HER2 status in patients with breast cancer before clinical decision. The Examiner further asserts that any one of Ross I, Baselga *et al.* (1996) or Baselga *et al.* (1999) teaches the clinical decision whether or not to treat breast cancer patients with HER2 antibody is based on HER2 status, and assessing HER2 status is determined using IHC. The Examiner urges that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute FISH technique for assessing the HER2 status before the treatment. As to claim 25, the Examiner relies on Baselga *et al.* (1999) for teaching that Herceptin® has shown efficacy in treating breast cancer overexpressing HER2.

Applicants submit that the presently claimed invention is patentable over the cited art.

The Instant Invention

The present invention concerns, at least in part, the surprising discovery that the response rate of HER2 amplified (*e.g.* FISH+) subjects unexpectedly exceeds the response rate of HER2 overexpressing (2+ and 3+) patients (page 29, lines 23-28). This lead to the conclusion in the present application that determining HER2 gene amplification is superior to determining HER2 protein overexpression for identifying patients who are more likely to benefit from HER2 antibody therapy. The surprising increase in likelihood of beneficial response was also seen in responses to chemotherapy plus Herceptin® (page 31, lines 7-12). Thus, whereas patients in the pivotal Herceptin® breast cancer trials were selected for therapy based on overexpression of HER2 at the 2+ or 3+ level by immunohistochemistry (IHC), and Herceptin® was approved in 1998 for therapy of such patients, the present invention has dramatically altered the conventional

wisdom concerning selecting breast cancer patients for therapy with a HER2 antibody.

Applicants submit that, before the present invention, it was counterintuitive that FISH would be superior to IHC in the context of antibody therapy, since IHC measures actual HER2 protein to which the HER2 antibody can bind, whereas FISH measures gene amplification which may, but does not necessarily, result in expressed protein to which the HER2 antibody can bind in order to confer a therapeutic benefit to the patient.

Prior to the instant invention, HER2 amplification had been studied with respect to disease prognosis (*i.e.* predicting the course of the disease), which is distinct from demonstrating efficacy upon treatment with a HER2 antibody. Even in the context of prognosis, the cited art shows that controversy existed as to the superior assay, if any. There was certainly no suggestion in the art that the FDA-approved method for selecting patients for therapy with a HER2 antibody by IHC was not the superior method.

Certainly, those patients selected for therapy based on HER2 gene amplification because of the present invention and thereby deriving the therapeutic benefits from administration of Herceptin® would agree that the instant invention represents an important advancement in the field of breast cancer therapy!

The "Detection Step" Prior Art References

The Examiner relies on Pauletti *et al.*, Ross II or Persons *et al.* as allegedly teaching the "detection step" of claim 21 herein.

Applicants submit that these references are primarily concerned with the use of FISH in a different context, namely prognosis, or predicting the course of disease, and would not have rendered the presently claimed invention obvious, even if combined with the other art.

Turning first to Pauletti *et al.*, this reference teaches away from the presently claimed invention by recognizing that FISH does not measure HER2 protein expression, and therefore cannot detect those cases which overexpress the gene product in the absence of gene amplification (col. 2 on page 68). Hence, Pauletti *et al.* would have suggested that patients with overexpression without amplification (though perhaps few) would be overlooked for therapy, if the IHC test was substituted by a FISH test. In any event, Pauletti *et al.* is

predominantly concerned with HER2 gene amplification as indicating the patient has a "poor clinical prognosis" (see the abstract), as opposed to selecting patients for therapy with a HER2 antibody based on HER2 gene amplification.

Turning now to Ross II, this fails to disclose or suggest the presently claimed method. In particular, while the Examiner asserts that Ross II teaches "Her2 gene amplification using FISH is superior to immunohistochemistry for assessing Her2 status in patients with breast cancer before clinical decision," Ross II is actually concerned with prognostic significance or HER2 gene in prostate carcinoma (as opposed to therapy of breast cancer). Even as to the use of HER2 amplification as an adverse prognostic factor in prostate cancer, Ross II acknowledges that additional clinical studies appear warranted (last paragraph, column 1 on page 2169).

The other detecting publication, Persons *et al.*, recognizes that the efficacy of Herceptin (Trastuzumab) has been confirmed in patients with overexpression of HER2, rather than amplification of HER2 (abstract). Persons *et al.* conclude only that HER2 amplification is an important prognostic and predictive marker in breast cancer, but provides no reasonable prediction as to whether evaluating HER2 amplification is superior (or even equivalent) to HER2 overexpression for selecting patients for therapy with a HER2 antibody.

The "Treating Step" Prior Art References

The Examiner relies on Ross I, Baselga *et al.* (1996) or Baselga et *al.* (1999) for teaching the clinical decision whether or not to treat breast cancer patients with HER2 antibody is based on HER2 status, and assessing HER2 status is determined using IHC.

Applicants agree that each of these three references teaches that IHC for measuring HER2 protein expression is the relevant test for selecting patients for therapy with a HER2 antibody. Applicants disagree that there is any suggestion or motivation in the references, even when combined with the other cited art, to simply substitute IHC with FISH.

Ross I is primarily concerned with the use of FISH to determine the "prognostic" significance of HER2 gene. For instance, the FISH studies in Table 2 on page 415 concern "HER-2 amplification more predictive than nodal status in young patients," "HER-2/*neu* gene amplification predicts recurrence and death," "3-tiered amplification system," or "HER-2 amplification predicted death independent

of nodal status," as opposed to the use of FISH in selecting patients for therapy with a HER2 antibody. As noted above, prognostic or predictive studies are distinct from determining whether a patient is disposed to respond favorably to a HER2 antibody, and treating a patient so-selected with a HER2 antibody.

Moreover, Ross I notes in column 1 on page 415 that "a significant discordance between HER2/neu abnormality detection methods has been described." In light of such discordance, Applicants submit it would not have been obvious to simply substitute FISH for the IHC method approved by the FDA for selecting breast cancer patients for therapy with Herceptin®.

The uncertainty in the art at the filing date is further underscored by the observation in Ross I that gene-based studies of HER2/neu gene amplification in breast cancer include a negative study (col. 1, first full paragraph on page 417 of Ross I), and that controversy exists over the best detection method (col. 1 on page 424).

In the final concluding paragraph, Ross I states that based "on the promising new information concerning the response of metastatic breast cancer in patients with HER-2/*neu* overexpressing primary tumors to treatment with anti-HER-2 antibodies (Herceptin®), it appears that further basic and clinical research studies of this gene and protein will likely continue well into the 21st Century." (Emphasis added, page 424). At best, this is an invitation to experiment, and in view of the uncertainty noted above, and the Examiner's acknowledgment, page 3, first paragraph of Office Action, that Ross I and II teach that breast cancer treatment requires undue experimentation, Applicants submit that, prior to the teachings in the present application, the presently claimed method would not have been obvious.

Applicants submit that Baselga *et al.* (1996) and (1999) fail to supply the deficiencies of the other references. Rather, these references teach away from the presently claimed invention. In both of these references describing actual human therapy with a HER2 antibody, the patient was only eligible for therapy if she overexpressed HER2 protein as determined by IHC (page 738 of Baselga (1996) under the heading *Selection of Patients*, and page 79 of Baselga (1999) under the heading *Patients*). There is nothing in the references to suggest that this selection step is optional or substitutable.

Conclusion

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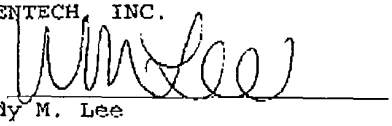
Applicants have demonstrated above how the cited art failed to disclose or suggest the presently claimed invention. The detection publications, were mainly concerned with prognosis or prediction, rather than selecting patients for therapy with a HER2 antibody. The treating references taught the importance of selecting HER2 overexpressing patients by IHC. Even if the above references did suggest therapy as claimed herein (which is denied), Applicants submit that the showing of unexpected results discussed above would provide objective evidence as to the nonobviousness of the presently claimed invention.

Applicants submit that this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,

GENENTECH, INC.

Date: June 24, 2004

By: 

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